REMARKS

Applicants wish to thank Examiner Collins, Bui and Housel for extending the courtesy of a telephonic interview with Applicants' representatives on November 1, 2002.

Following entry of the instant amendment, claims 53, 56, 63-65, 67, 68, and 76-84 will be pending in the case. Support for "a plant cell" in claim 53 is found throughout the specification. The requirement in claim 53 that plant cells not contain nucleotide sequence encoding an immunoglobulin heavy chain finds support throughout the specification, Example 2 beginning at page 64 and Table 3 at page 68 being typical. New claims 77-84 also find support in the application as filed. Accordingly, the amendments and new claims raise no issue of new matter.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 53, 63-68 and 76 have been rejected under 35 U.S.C. § 112, first paragraph for lacking written description for the phrase "at least a portion of the variable region of an immunoglobulin light chain." The Examiner alleges that this phrase introduces new matter that goes beyond the specification which is alleged to cover only specific antibody fragments previously known in the art. The rejection is respectfully traversed.

To satisfy the written description requirement of 35 U.S.C. § 112, ¶ 1, the specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the claimed invention. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. *See, e.g., Enzo Biochem. Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1612 (Fed. Cir. 2002).

The language at issue, "at least a portion of the variable region of an immunoglobulin light chain," cannot be new matter because one can find this language literally or nearly so at multiple sites in the patent specification. For example, the

specification, page 11, lines 5-12 (emphasis added) uses this phrase in reference to an Fv fragment.

> Fv fragment: A multimeric protein **consisting of the immunologically active portions of an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region** covalently coupled together and capable of specifically combining with antigen. Fv fragments are typically prepared by expressing in suitable host cell **the desired portions of immunoglobulin heavy chain variable region and immunoglobulin light chain variable region** using methods well known in the art.

See also page 15, lines 28-33 (emphasis added).

> In yet another embodiment, the present transgenic plant contains a multimeric protein that is a Fv fragment comprised of at least a portion of an immunoglobulin heavy chain variable region and **at least a portion of an immunoglobulin light chain variable region**. The immunoglobulin heavy and light chain variable regions autogenously associate with each other within the plant cell to assume a biologically active conformation having a binding site specific for a preselected or predetermined antigen.

Further support is found at page 16, lines 11-18 (emphasis added).

> When the multimeric protein produced in accordance with the present invention is an abzyme comprised of at least a portion of the immunoglobulin heavy chain variable region in association with another polypeptide chain, **this other polypeptide chain includes at least the biologically active portion of an immunoglobulin light chain variable region**. Together, these two polypeptides assume a conformation having a binding affinity or association constant for a preselected ligand that is different, preferably higher, than the affinity or association constant of either of the polypeptides alone, i.e., as monomers.

Thus, in no less than three places, the specification provides literal or near literal support for the limitation in question.

Furthermore, Applicants takes issue with the rationale upon which the rejection is based. The Examiner argues that the claim language in question encompasses polypeptides with as "few as one amino acid." (Office Action, p.4). However, this is impossible because the claim requires that the expressed polypeptide be capable of forming an antigen-specific immunoglobulin when co-expressed in a plant cell with a heavy chain. Thus, the Examiner's rationale for a single amino acid polypeptide has meaning only when taken out of context form the rest of the claim.

The Examiner also argues that the limitation in question encompasses "at least one amino acid less than a full length polypeptide." Applicants agree and point out that one amino acid less than a full polypeptide is "at least a portion of the variable region," Thus, this argument does not support a new matter rejection.

Applicants further take issue with the view that one skilled in the art would understand Applicants' disclosure to be limited solely to specific antibody fragments that were known in the art. (Office Action, page 4). In addition to being unsupported, this statement directly contradicts the extensive body of literature on antibody engineering that existed throughout the 1980s. This view is exemplified in Applicants' specification at page 3, lines 1-6 (emphasis added)..

> One of the most useful aspects of using a recombinant expression system for antibody production is the ease with which the antibody can be tailored by molecular engineering. **This allows the production of antibody fragments and single-chain molecules, as well as the manipulation of full-length antibodies.** For example, a side [sic] range of functional recombinant-antibody fragments, such as Fab, F_v, single-chain and single-domain antibodies, may be generated.

This broad ranging suggestion to engineer immunoglobulins is reflective of the art as a whole. For example, U.S. Patent no. 4,816,567 to Cabilly et al., filed in 1983 describes a

wide variety of antibody fragments that go well beyond those available by proteolytic processing. The Summary of the Invention of the Cabilly patent is shown with emphasis below.

> The invention relates to antibodies and to non-specific immunoglobulins (NSIs) formed by recombinant techniques using suitable host cell cultures. . . .
>
> Finally, either the light chain or heavy chain alone, **or portions thereof**, produced by recombinant techniques are included in the invention and may be mammalian or chimeric.

Cabilly also defines "altered antibodies" at col. 7, beginning at line 7. The definition states as follows with respect to the power of recombinant technology (emphasis added):

> Because of the relevance of recombinant DNA techniques to this invention, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. **The possible variations are many and range from changing of just one or a few amino acids to the complete redesign, for example, the constant region.**

Cabilly further elaborates on "altered antibodies" in the context of chimeric antibodies at col. 15, beginning at line 35 (emphasis added).

> Altered antibodies present, in essence, an extension of chimeric ones. Again the techniques of D.1 and D.2 are applicable; however, rather than splicing portions of chain(s), the **suitable amino acid alterations, deletions or additions** are made using available techniques such as mutagenesis (supra).

Thus, immunoglobulin chains under Cabilly may be modified by alteration, deletion or addition of amino acids.

Further, U.S. Patent No. 4,704,692 to Ladner (cited on page 28 lines 5-13 of the instant application) filed in 1986 teaches that recombinant methods can be used to express unique fragments of immunoglobulins in which terminal amino acids at the N- or C-terminus of the variable region of light or heavy chains are removed as part of the strategy for linking the chains with a peptide linker to form a single chain Fv fragment.

Thus, the evidence does not support the Examiner's contention that one skilled in the art would understand Applicants' disclosure to be limited solely to specific antibody fragments that were known in the art. The claim language at issue, "at least a portion of the variable region of an immunoglobulin light chain" is well supported in the specification, as already shown and the ordinary skilled artisan would have been quite familiar with such engineered immunoglobulins. It is true that the specification discusses well known fragments as preferred embodiments, but there is no attempt to limit the invention to such embodiments and any attempt to do so is improper. *See Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 987, 6 USPQ2d 1601, 1605 (Fed.Cir.1988) ("Where a specification does not require a limitation, that limitation should not be read from the specification into the claims."). Accordingly, the rejection for new matter under section 112, first paragraph, is without basis and should be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of Claim 53 under 35 U.S.C. § 112, second paragraph as being indefinite because "sequence" in part (b) allegedly lacks antecedent basis in the term "sequences" in part (a), is respectfully traversed. Although Applicants believe that the claim is clear, the amendment has been made to further prosecution in the case.

The rejection of Claim 53 under 35 U.S.C. § 112, second paragraph as being indefinite because "said light polypeptide product" in part (b) allegedly lacks antecedent basis in part (a), is respectfully traversed. Although Applicants believe that the claim is clear, amendment to "said light chain" has been made to further prosecution in the case.

The rejection of Claim 53 under 35 U.S.C. § 112, second paragraph as being indefinite because "derived" is allegedly unclear as to how much of the light chain is derived, is respectfully traversed. It is noted that there is no basis given for why this term is unclear. "Derived" is not indefinite because the skilled artisan would understand that this term properly reflects that various lengths of light chain are encompassed under the claim by virtue of the limitation "at least a portion of the variable region of an immunoglobulin light chain. When one skilled in the art would understand all of the

language in the claims when read in light of the specification, a claim is not indefinite. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984); *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Accordingly, the rejection is without basis and should be withdrawn.

REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 53, 56 and 63 under 35 U.S.C. § 102(b) as being allegedly anticipated by the During Dissertation for reasons set forth in the Office Action of November 20, 2001, is respectfully traversed. The examiner appears to have misunderstood the reference. As was pointed out previously by Applicant and by Dr. Richard Lerner, During transformed plant cells with an expression vector that encoded an immunoglobulin light chain but not a heavy chain. However, During was unable to detect any expressed light in the cells. During dissertation, p. 80, line 2; see Lerner Declaration, ¶¶13, 25 ("The During Dissertation also fails to teach how to successfully use plant cells to express a heavy chain or light chain polypeptide, but not both, in plant cells.") Thus, there is no basis on which the During Dissertation can anticipate the claims.

Applicants does not know why During failed to produce light chain from his light chain only vector. When During transformed plant cells with an expression vector encoding both a heavy and a light chain, he reported that some light chain was produced. According to Dr. Richard Lerner, During failed to detect the light and heavy chain from the double chain vector by direct Western blotting but allegedly detected a processed light chain but not a heavy chain by indirect Western blotting. Lerner Declaration, ¶ 15. Lerner, however, leaves open the possibility that During's allegedly successful light chain expression data may be the result of artifact. Lerner Declaration, ¶ 16; see also ¶ 18 and 19 discussing unexplained cell staining results for detecting light chain expression.

Thus, During did not know why he failed to produce light chain in plants transformed with a vector that encoded light but not heavy chain, and although During asserted that light chain was produced from his double chain vector, these results are

open to serious scientific question. During made no attempt understand these failures experimentally and offered no explanations.

Another ground on which the During Dissertation fails as an anticipatory reference involves the claim requirement for the light chain (or portion of a variable region) to be capable of forming an antigen-specific immunoglobulin when co-expressed with a heavy chain in a plant cell. The During Dissertation cannot meet this requirement because During failed to convincingly demonstrate heavy expression or heavy and light chain assembly in plant cells. *See* Lerner declaration, ¶¶ 15-19. The argument that During's light chain is from an anti-NP IgM antibody known to be produced by mammalian lymphoid cells is without relevance because the claim requires that the light chain be produced in plant cells. Thus, there are separate and independent grounds upon which to negate the rejection.

Applicant takes issue with the Examiner's position that the expression in a plant cell of a heterologous polypeptide having a leader sequence which is cleaved following proteolytic processing would have been within the limits of one skilled in the art at the time of Applicants invention. First, it is respectfully submitted that this argument is entirely irrelevant to the question of anticipation. Second, the argument lacks foundation to the extent that it is applied to expressing an immunoglobulin heavy or a light chain in plants. The argument appears to be based on the Goodman patent. However, Goodman's apparent success in producing interferon, a protein that normally is produced a single polypeptide, would not have been considered to translate to a single polypeptide of a dual chain heterodimer protein such as immunoglobulin. The Lerner Declaration supports as much when it stated that "the ability to express each individual chain (light or heavy) was unexpected . . . ." Lerner Declaration, ¶ 25. Furthermore, as already demonstrated, During's clear failure to obtain light-chain expression in plant cells transformed with a light chain only vector is direct evidence against the view that an immunoglobulin light chain having a leader sequence which is cleaved following proteolytic processing and expressed in the absence of heavy chain encoding nucleotide sequence would have been within the limits of one skilled in the art.

Accordingly, for all the above reasons, the rejection of the claims as allegedly being anticipated by the During Dissertation is without basis and should be withdrawn.

REJECTION UNDER 35 U.S.C. § 102 OVER GOODMAN

The rejection of claims 53, 56, 63, 64, 67, 68 and 76 under 35 U.S.C. § 102(b) as allegedly being anticipated by Goodman (U.S. Patent no. 4,956,282) is respectfully traversed. The Examiner asserts that Goodman teaches transformation of plant cells with a mammalian gene including nucleotide sequence encoding light chain. However, Goodman cannot anticipate the claims because the reference fails to describe a plant cell that contains nucleic acid encoding at least a portion of a light chain variable region but not a heavy chain. Goodman does not even consider the possibility that light chains may be expressed by themselves. Thus, Goodman fails as an anticipatory reference on this basis alone.

Another indepdent ground on which Goodman fails as an anticipatory reference involves the claim requirement for the light chain (or portion of a variable region) to be capable of forming an antigen-specific immunoglobulin when co-expressed with a heavy chain in a plant cell. Goodman cannot meet this requirement because the reference does not consider expressing the light chain alone in a plant.

Furthermore, as previously pointed out by Applicant, Goodman's mere passing reference in a single paragraph to expressing immunoglobulin amidst a "wish list" of desired applications extrapolated from a singe example is simply not enabling for antibody expression of a heterodimer, let alone a single immunoglobulin chain. Goodman's apparent success in producing interferon would not have been considered to translate to a single polypeptide of a dual chain protein such as immunoglobulin. The Lerner Declaration supports as much when it stated that "the ability to express each individual chain (light or heavy) was unexpected . . . ." Lerner Declaration, ¶ 25. Furthermore, as already demonstrated, During's clear failure to obtain light chain expression in plant cells transformed with a light chain only vector is direct evidence against the view that

heterologous polypeptide having a leader sequence which is cleaved following proteolytic processing would have been within the limits of one skilled in the art.

Accordingly, for all the above reasons, the rejection of the claims as allegedly being anticipated by Goodman is without basis and should be withdrawn.

REJECTION UNDER 35 U.S.C. § 103 OVER DURING

The Examiner's decision to withdraw the obviousness rejection of During with respect to claims 53-64 and 66 is noted and greatly appreciated. However, the decision to maintain the rejection with respect to claim 65 is perplexing. Claim 65 is a dependent claim that requires the plant cell to be from an alga. The rejection provides no clue as to why this claimed feature is obvious when independent claim 53 or any other claims is nonobvious. It is well known that if an independent claim is invalid as obvious, dependent claims by virtue of their additional limitations cannot be presumed to be invalid. Sandt, 264 F.3d at 1356, 60 USPQ2d at 1098 ("Because dependent claims contain additional limitations, they cannot be presumed to be invalid as obvious just because the independent claims from which they depend have been properly so found."). However, Applicants are aware of no law by which a dependent claim is obvious when the independent claim is nonobvious. It stands to reason that adding one or more limitations to a nonobvious invention cannot render such invention obvious. Accordingly, the rejection of claim 65 as obvious over the During Dissertation fails to state a prima facie case, and is without basis in view of Applicants' previous arguments and should be withdrawn.

Although not needed to support Applicants' position, it is noted that During also fails to teach or suggest the claim requirement for the light chain (or portion of a variable region) to be capable of forming an antigen-specific immunoglobulin when co-expressed with a heavy chain in a plant cell. During cannot meet this requirement because the reference does not consider expressing the light chain alone in a plant and does not succeed in producing an assembled antibody in plants.

It is finally noted that During's failed attempt to express a light chain from a vector that does not encode a heavy chain constitutes a teaching away that further negates any obvious rejection based on the During Dissertation and/or any other reference of record. In sum, the rejection of claim 65 as being obvious over the During Dissertation is improper and without basis and should be withdrawn.

REJECTION UNDER 35 U.S.C. § 103 OVER GOODMAN

The rejection of claim 65 under 35 U.S.C. § 103(a) as being allegedly anticipated by Goodman is respectfully traversed. It is noted that this rejection is newly applied and is not applied to independent claim 53. It is believed that the failure to apply this rejection to the independent claim was not a clerical error as the same was done in the obviousness rejection over During in which the Examiner affirmatively stated that the independent claim was nonobvious. As will be discussed below, Applicant asserts that all the claims (including claim 65) are nonobvious over Goodman, and the examiner is reminded that there is no legal basis on which to hold claim 65 as obvious when independent claim 53 which is nonobvious.

As already mentioned under anticipation, Goodman fails to even mention let alone teach or suggest the requirement for a plant cell containing nucleotide sequence encoding at least a portion of the variable region of a light chain but not a heavy chain. Goodman's one sentence reference to immunoglobulins sandwiched amongst a wish list of desired applications is simply non-enabling.

Furthermore, Goodman's apparent success with expressing gamma interferon would not reasonably have been considered to advance the possibility of expressing at least a portion of a light chain variable region from cells that do not contain nucleotide sequence encoding a heavy chain. Gamma interferon is structurally and functionally distinct from an immunoglobulin light or heavy chain. Interferon is naturally a single polypeptide while an immunoglobulin light chain is a member of an immunoglobulin heterodimer. The Lerner Declaration supports as much when it stated that "the ability to

express each individual chain (light or heavy) was unexpected . . . ." Lerner Declaration, ¶ 25.

Although not needed to support Applicants position, Goodman also fails to teach or suggest the claim requirement for the light chain (or portion of a variable region) to be capable of forming an antigen-specific immunoglobulin when co-expressed with a heavy chain in a plant cell. Goodman cannot meet this requirement because the reference does not consider expressing the light chain alone in a plant and does not attempt let alone succeed in producing an assembled antibody in plants.

It is finally noted that During's failed attempt to express a light chain from a vector that does not encode a heavy chain as discussed above constitutes a teaching away that further negates any obvious rejection based on the Goodman patent and/or any other reference of record. In sum, the rejection of claim 65 as being obvious over Goodman is improper and without basis and should be withdrawn.

PETITION TO NULLIFY A TERMINAL DISCLAIMER

Filed concurrently with the instant Amendment is a Petition to nullify a terminal disclaimer filed in the case under 37 C.F.R. § 1.182. A double patenting rejection over U.S. Patent Nos. 5,959,177, 5,639,947 and 5,202,422 was made in an Office Action mailed November 11, 2001 and was later withdrawn in view of a Terminal Disclaimer filed by Applicant on March 18, 2002. The reasons for withdrawal stated in the Petition are copied below for convenient reference by the Examiner.

Briefly, an obvious-type double patenting rejection was made over instant claims 53-66 for U.S. Patent Nos. 5,959,177, 5,639,947 and 5,202,422 in an Office Action dated November 11, 2001. Applicant filed a Terminal Disclaimer to remove the rejection on March 18, 2002. The Terminal Disclaimer was approved and the rejection withdrawn in an Office Action dated August 13, 2002.

This request to nullify the Terminal Disclaimer is based on amendments made to the claims that eliminate any purpose for having the Terminal Disclaimer. Prosecution to date has resulted in cancellation of claims 54, 55, 57-62, and 66. This leaves only claims 53; 56, and 63-65 remaining in the case that were subject to the rejection. Of these claims only claim 53 is independent. Claim 53 as it existed at the time of the obvious-type double patenting rejection is shown below (see Preliminary Amendment of February 24, 2000).

> 53. A plant cell containing (a) nucleotide sequence encoding an immunoglobulin product containing at least a portion of an immunoglobulin light chain and (b) the immunoglobulin product encoded by said nucleotide sequences.

Instant claim 53 as presently amended is shown below.

> 53. (Amended three times) A plant cell containing:
>
> (a) nucleotide sequence encoding an immunoglobulin product comprising at least a portion of the variable region of an immunoglobulin light chain and a leader sequence forming a secretion signal, said light chain derived from an antigen-specific immunoglobulin comprising a heavy and light chain, and;
>
> (b) immunoglobulin product encoded by said nucleotide sequence wherein said leader sequence is cleaved from said immunoglobulin light chain following proteolytic processing, said light chain being capable of forming an antigen-specific immunoglobulin when co-expressed in a plant cell with said heavy chain from said antigen-specific immunoglobulin wherein said plant cell does not contain nucleotide sequence encoding said immunoglobulin heavy chain.

The difference between claim 53 as first filed versus as currently amended is shown below.

> 53. (Amended three times) A plant cell containing:
>
> (a) nucleotide sequence encoding an immunoglobulin product [containing] comprising at least a portion of the variable region of an immunoglobulin light chain and a leader

sequence forming a secretion signal, said light chain derived from an antigen-specific immunoglobulin comprising a heavy and light chain, and;

(b) immunoglobulin product encoded by said nucleotide [sequences] sequence wherein said leader sequence is cleaved from said immunoglobulin light chain following proteolytic processing, said light chain being capable of forming an antigen-specific immunoglobulin when co-expressed in a plant cell with said heavy chain from said antigen-specific immunoglobulin wherein said plant cell does not contain nucleotide sequence encoding said immunoglobulin heavy chain.

It is readily apparent that substantial amendment has occurred following issuance of the obvious-type double patenting rejection. With this background established, Applicant will now address the propriety of the terminal disclaimer with respect to each referenced patent.

1. U.S. Patent Nos. 5,959,177

Claims 53-66 were rejected on November 11, 2001 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 6-12 of U.S. Patent No. 5,959,177. It was alleged that the conflicting claims were not patentably distinct because the transgenic plant comprising nucleotide sequences encoding immunoglobulin heavy and light chain polypeptides of U.S. Patent No. 5,959,177 would encompass the cells containing nucleotide sequences encoding the immunoglobulin products of claims 53-66 of the instant application.

Claims 6-12 of U.S. Patent No. 5,959,177 (the '177 patent) are directed to a transgenic plant containing nucleotide sequence encoding one or more immunoglobulin heavy-chain polypeptides. Claim 6 of the '177 patent is shown below.

6. A transgenic plant comprising:

a. plant cells that contain a nucleotide sequence encoding one or more immunoglobulin heavy-chain polypeptides, a nucleotide sequence encoding a polypeptide linker or joining

chain, and a nucleotide sequence encoding a secretory component; and

b. immunologically active secretory antibodies encoded by said nucleotide sequences.

Notably, claims 6-12 of the '177 patent require the transgenic plant cells to include nucleotide sequence encoding a heavy chain immunoglobulin. This is in contrast to instant claims 53, 56, and 63-65 which, as shown above, expressly exclude cells with such nucleotide sequence. Thus, there is no overlap between instant claims 53, 56, and 63-65 and claims 6-12 of the '177 patent. These two claim sets also should be separately patentable over the other for several reasons. First, a cell expressing the light chain alone is much different from a cell that expresses both a light and a heavy chain since the light chain is normally produced only in combination with a particular heavy chain which together form a heterodimer. In addition, at the time of the invention, antibodies were not known to be expressed by plants and there was a prejudice in the art against this possibility. This prejudice has been established by the Declaration of Richard Lerner, of record in the case. Lerner Declaration, ¶¶ 3-8.

> [T]here was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed).

Further supporting Applicant's position is the During Dissertation over which the claims have been rejected. As argued by Applicant, During attempted but failed to express an immunoglobulin light chain in plants which did not contain nucleotide sequence encoding a heavy chain. During's result suggests unique problems with achieving light chain expression when the heavy chain gene is absent from the cell, arguing for separate

patentability of light chain expression alone versus expression of the immunoglobulin heterodimer.

Consistent with this view is the position taken by the Patent Office which issued a restriction requirement in this case on July 5, 2001 (made final an November 20 ,2001). The restriction divided the claims into three groups: Group I: drawn to plant cells containing nucleic acid encoding both a heavy chain and light chain, Group II , drawn to plant cells containing nucleic acid encoding a heavy chain; and Group III, drawn to plant cells containing nucleic acid encoding a light chain. The rationale offered to support the restriction rested on the separate patentability of these three groups.

> The inventions are distinct, each from the other because of the following reasons: Inventions I and (II &III) are related as combination and subcombinations. Inventions of this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the combination recites 2 distinct subcombinations, the immunoglobulin heavy chain nucleotide sequence and the immunoglobulin light chain nucleotide sequence. Since both of these subcombinations is separately claimed, each serves as evidence that the other subcombination when combined is not the sole basis for patentability of the invention. The subcombination has separate utility such as for the production of heavy or light chain. Because these inventions are distinct for the reasons given above and the literature search required for one Group is not required for another Group, restriction for examination purposes as indicated is proper.

Thus, the position taken by the Patent Office to restrict the claims in this case is fully consistent with Applicant's arguments on behalf of this Petition to nullify the terminal disclaimer, (and is inconsistent with the original obviousness-type double patenting rejection). For all the above reasons, it is respectfully submitted that the Terminal Disclaimer is no longer necessary or appropriate for claims 6-12 of the '177 patent.

2. U.S. Patent Nos. 5,639,947

Claims 53-66 were rejected on November 11, 2001 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-7 of U.S. Patent No. 5,639,947. It was alleged that the conflicting claims were not patentably distinct because the transgenic plant comprising nucleotide sequences encoding immunoglobulin heavy and light chain polypeptides of U.S. Patent No. 5,639,947 would encompass the cells containing nucleotide sequences encoding the immunoglobulin products of claims 53-66 of the instant application.

Claims 1-7 of U.S. Patent No. 5,639,947 (the '947 patent) are directed to a transgenic plant containing nucleotide sequence encoding an immunoglobulin heavy and light chain polypeptides. Claim 1 of the '947 patent is shown below.

> 1. A transgenic plant comprising:
>
> (a) plant cells containing nucleotide sequences encoding immunoglobulin heavy- and light-chain polypeptides that each contain an immunoglobulin leader sequence forming a secretion signal; and
>
> (b) immunologically active immunoglobulin molecules encoded by said nucleotide sequences.

Notably, claims 1-7 of the '947 patent require the transgenic plant cells to include nucleotide sequence encoding a heavy chain immunoglobulin. This is in contrast to instant claims 53, 56, and 63-65 which, as shown above, expressly exclude cells with such nucleotide sequence. Thus, there is no overlap between instant claims 53, 56, and 63-65 and claims 1-7 of the '947 patent. Furthermore, these two claim sets also should be separately patentable over the other for same reasons as discussed above for claims 6-12 of the '177 patent. For all the above reasons, it is respectfully submitted that the Terminal Disclaimer is no longer necessary or appropriate for claims 1-7 of the '947 patent.

3. U.S. Patent Nos. 5,202,422

Claims 53-66 were rejected on November 11, 2001 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-3 of U.S. Patent No. 5,202,422. It was alleged that the conflicting claims were not patentably distinct because the plant cell composition and immunologically active glycosylated immunoglobulin of claims 1-3 of U.S. Patent No. 5,202,422 would encompass the cells containing nucleotide sequences encoding the immunoglobulin products of claims 53-66 of the instant application.

Claims 1-3 of U.S. Patent No. 5,202,422 (the '422 patent) are directed to a plant cell composition comprising a glycosylated immunoglobulin molecule free of sialic acid. Claim 1 of the '422 patent is shown below.

> 1. A composition comprising a glycopolypeptide multimer and plant material, wherein said multimer comprises an immunologically active glycosylated immunoglobulin molecule free of sialic acid residues

It is well known that an immunoglobulin molecule that is a multimer is a reference to an immunogloublin with at least a heavy chain variable region or immunologically active portion thereof and at least a light chain or immunologically active portion thereof containing heterodimer. Thus, common to claims 1-3 of the '422 patent is the requirement for a heavy chain immunoglobulin. This is in contrast to instant claims 53, 56, and 63-65 which, as shown above, expressly exclude cells with nucleotide sequence encoding a heavy chain immunoglobulin. Thus, there is no overlap between instant claims 53, 56, and 63-65 and claims 1-3 of the '422 patent. Furthermore, these two claim sets also should be separately patentable over the other for same reasons as discussed above for claims 6-12 of the '177 patent. For all the above reasons, it is respectfully submitted that the Terminal Disclaimer is no longer necessary or appropriate for claims 1-3 of the '422 patent.

It is believed that the Applicant has thoroughly explained why the Terminal Disclaimer is longer useful or appropriate for any of the listed patents. As suggested under MPEP §1490(A), relief is appropriate when, such as in this case, the Terminal Disclaimer

does not take effect because the patent has not been granted and the public has not had the opportunity to rely on the Terminal Disclaimer. Thus, for all the above reasons, it is respectfully requested, that the Petition to nullify the Terminal Disclaimer be granted.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING

The provisional rejection of the claims for obvious-type double patenting over copending patent applications is respectfully traversed.

1. Provisional Rejection over U.S. Patent Application No. 09/200657

Claims 53, 56, 63-68 and 76 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 43, 44, 48, 53, 57-59, 79, 81-90 and 93-99 of copending Application No. 09/200657. It is alleged that that conflicting claims are not patentably distinct because the plant cells comprising at least a portion of the variable region of an immunoglobulin light chain of the instant application would encompass the transgenic plants comprising plant cells containing a nucleotide sequence encoding an antigen-specific immunoglobulin single polypeptide product of application no. 09/200657.

Claim 43, which is an independent claim of Application No. 09/200657, is shown below as presently amended.

> 43 (Three times amended) A plant, comprising plant cells containing:
>
> a) nucleotide sequences encoding an antigen-specific immunoglobulin single polypeptide product containing at least an immunoglobulin heavy chain polypeptide or portion thereof and an immunoglobulin light chain or portion thereof and encoding a peptide linker therebetween, wherein said nucleotide sequences encode a leader sequence forming a secretion signal for said single polypeptide product; and

b) antigen-specific immunoglobulin single polypeptide product encoded by said nucleotide sequences, wherein said leader sequence is cleaved from said polypeptide product following proteolytic processing and assembly.

As indicated, copending claim 43 requires the nucleotide sequence to encode antigen-specific immunoglobulin single polypeptide product which includes at least an immunoglobulin heavy chain polypeptide or portion thereof. In contrast, claims 53, 56, 63-68 and 76, as discussed, exclude transgenic plant cells with such nucleotide sequence. Thus, there is no overlap between these groups of claims.

Claim 83 is another independent claim of Application No. 09/200657 over which obvious-type double patenting has been alleged. The claim is shown below as presently amended (Amendment filed concurrently with the instant Amendment).

83. (Amended) A plant, comprising plant cells containing:

a) nucleotide sequence encoding an immunoglobulin single polypeptide product containing an immunoglobulin heavy chain polypeptide, wherein said nucleotide sequence encodes a leader sequence forming a secretion signal for said single polypeptide product, said heavy chain derived from an antigen-specific immunoglobulin comprising a heavy and light chain, and said single polypeptide product being capable of forming an antigen-specific immunoglobulin when co-expressed in the same cell with said light chain from said antigen-specific immunoglobulin; and

b) immunoglobulin single polypeptide product encoded by said nucleotide sequences, wherein said leader sequence is cleaved from said polypeptide product following proteolytic processing of said single polypeptide product.

As indicated, copending claim 83 requires the nucleotide sequence to encode immunoglobulin single polypeptide product which contains an immunoglobulin heavy chain polypeptide. Thus, claim 83 and its dependent claims 83-90 and 93-99 require cells that contain nucleotide sequence encoding a heavy chain. In contrast, claims 53, 56, 63-68 and 76, as discussed, exclude transgenic plant cells with such nucleotide sequence. Thus, there is no overlap between these groups of claims.

Furthermore, copending claims 43, 44, 48, 53, 57-59, 79, 81-90 and 93-99 would be patentably distinct over instant claims 53, 56, 63-68 and 76, for the reasons discussed above in the Petition to nullify the terminal disclaimer with respect to the '177 patent. It is concluded, therefore, that copending claims 43, 44, 48, 53, 57-59, 79, 81-90 and 93-99 are not obvious over claims 53, 56, 63-68 and 76 of the instant application. Accordingly, withdrawal of the rejection is respectfully requested.

2. Provisional Rejection over U.S. Patent Application No. 09/200657

Claims 53, 56, 63-68 and 76 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 21, 24-40, 43, 50, 54-64, 69 and 80 of copending Application No. 09/512,568. It is alleged that that conflicting claims are not patentably distinct because the plant cells containing nucleotide sequence encoding at least a portion of the variable region of an immunoglobulin light chain of the instant application would encompass the plant cells containing nucleotide sequence encoding an antigen-specific immunoglobulin of application no. 09/512,568. The rejection is respectfully traversed.

Claim 21 which is an independent claim of Application No. 09/512,568 is shown below as presently amended.

> 21. (Amended three times) A plant cell comprising:
>
> (a) plant cells containing nucleotide sequences encoding a biologically functional multimeric protein comprising at least two different polypeptides not normally produced by plants, wherein each nucleotide sequence encoding a polypeptide of the multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said polypeptide following proteolytic processing and
>
> (b) biologically functional multimeric proteins encoded by said nucleotide sequences formed by assembly of said polypeptides in the cell.

Thus, copending claims 21, and 24-40 require the cells to contain nucleotide sequence encoding a biologically functional multimeric protein comprising at least two different polypeptides not-normally produced by plants. Encompassed within the term "multimeric protein" are immnoglobulins with contain a heavy and a light chain. Thus, copending claims 21 and 24-40 encompass cells containing nucleotide sequence encoding an immunogloublin heavy chain. In contrast, claims 53, 56, 63-68 and 76, as discussed, encompass cells that exclude such nucleotide sequence. Thus, there is no overlap between these groups of claims.

Claim 43 is another independent claim of Application No. 09/512,568 over which obviousness-type double patenting has been alleged. The claim is shown below as presently amended.

> 43. (Amended) A plant cell containing nucleotide sequences encoding an antigen-specific immunoglobulin, said nucleotide sequences encoding an immunoglobulin heavy and light chain polypeptide wherein each polypeptide contains a leader sequence that forms a secretion signal; and immunoglobulin encoded by said nucleotide sequences, wherein each leader sequence is cleaved from said immunoglobulin heavy chain and light chain polypeptide following proteolytic processing resulting in assembly of said antigen-specific immunoglobulin.

Thus, copending claims 43, 50, 54-64, 69 and 80 require the cells to contain nucleotide sequence encoding an immunoglobulin heavy chain. In contrast, claims 53, 56, 63-68 and 76, as discussed, encompass cells that exclude such nucleotide sequence. Thus, there is no overlap between these groups of claims.

Furthermore, copending claims 21, 24-40, 43, 50, 54-64, 69 and 80 would be patentably distinct over instant claims 53, 56, 63-68 and 76, for the reasons discussed above in the Petition to nullify the terminal disclaimer with respect to the '177 patent. It is concluded, therefore, that copending claims 21, 24-40, 43, 50, 54-64, 69 and 80 are not obvious over claims 53, 56, 63-68 and 76 of the instant application. Accordingly, withdrawal of the rejection is respectfully requested.

3. Provisional Rejection over U.S. Patent Application No. 09/717888

Claims 53, 56, 63-68 and 76 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 72, 78 and 79 of copending Application No. 09/717,888. It is alleged that the conflicting claims are not patentably distinct because the plant cell expressing a multimeric protein of copending Application No. 09/717,888 would encompass the plant cells containing nucleotide sequence encoding an antigen-specific immunoglobulin of application no. 09/717,888. The rejection is respectfully traversed.

If the multimeric protein of claims 72, 78 and 79 of copending Application No. 09/717,888 can be interpreted to include an immunogloublin heavy chain, then such claims would not overlap with instant claims 53, 56, 63-68 and 76 since the latter claims exclude cells with heavy chain encoding nucleotide sequence. Furthermore, the copending claims 72, 78 and 79 and instant claims 53, 56, 63-68 and 76 should not be obvious over the other for the reasons discussed above in the Petition to nullify the terminal disclaimer with respect to the '177 patent. Accordingly, withdrawal of the rejection is respectfully requested.

4. **Provisional Rejection over U.S. Patent Application No. 09/982107**

Claims 53, 56, 63-68 and 76 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 86 of copending Application No. 09/982,107. It is alleged that the conflicting claims are not patentably distinct because the transgenic tobacco plant that comprises nucleotide sequence encoding IgG of copending Application No. 09/982,107 would be composed of plant cells containing nucleotide sequence encoding an antigen-specific immunoglobulin of application no. 09/982,107. The rejection is respectfully traversed.

Claim 86 of copending Application No. 09/982,107 specifies that the tobacco plant comprises nucleotide sequences encoding an "IgG immunoglobulin." It is well known in the art that an IgG immunoglobulin is a tetramer composed of two gamma heavy chains,

each associated with a light chain. Thus, claim 86 requires the plant to contain nucleotide sequence encoding a heavy chain. In contrast, claims 53, 56, 63-68 and 76, as discussed, encompass cells that exclude such nucleotide sequence. Thus, there is no overlap between the instant claim group and copending claim 86.

Furthermore, copending claim 86 would be patentably distinct over instant claims 53, 56, 63-68 and 76, for the reasons discussed above in the Petition to nullify the terminal disclaimer with respect to the '177 patent. It is concluded, therefore, that copending claim 86 is not obvious over claims 53, 56, 63-68 and 76 of the instant application. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: November 13, 2002

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

53. (Amended three times) A plant cell containing:

(a) nucleotide sequence encoding an immunoglobulin product comprising at least a portion of the variable region of an immunoglobulin light chain and a leader sequence forming a secretion signal, said light chain derived from an antigen-specific immunoglobulin comprising a heavy and light chain, and;

(b) immunoglobulin product encoded by said nucleotide [~~sequences~~] **sequence** wherein said leader sequence is cleaved from said immunoglobulin light chain following proteolytic processing, said light **chain** [~~polypeptide product~~] being capable of forming an antigen-specific immunoglobulin when co-expressed in [~~the same~~] **a plant** cell with said heavy chain from said antigen-specific immunoglobulin **wherein said plant cell does not contain nucleotide sequence encoding said immunoglobulin heavy chain**.